

**FACILE PREPARATION OF
1-HYDROXY-1,2-BENZIODOXOL-3(1*H*)-ONE 1-OXIDE (IBX) AND
DESS–MARTIN REAGENT USING SODIUM HYPOCHLORITE UNDER
CARBON DIOXIDE**

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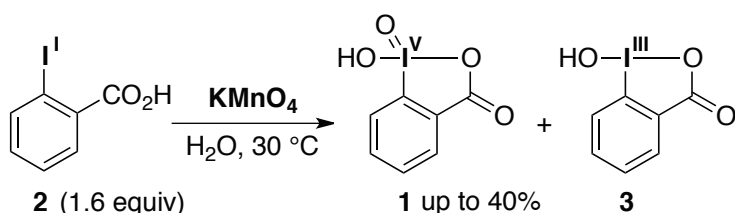
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Abstract – We have developed a safe, convenient, and inexpensive method for preparation of the widely used oxidizing agent 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX), by treatment of 2-iodobenzoic acid with aqueous sodium hypochlorite under CO₂ at room temperature. As the only by-product is NaCl, this reaction can be utilized for one-pot synthesis of 1,1,1-triacetoxy-1,2-benziodoxol-3(1*H*)-one (Dess-Martin reagent) in excellent yield.

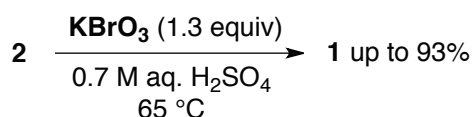
Since its first discovery in 1893^{1a} and later re-evaluation by Frigerio and Santagostino *et al.* in 1994,^{1b} 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (commonly known as IBX) (**1**) has been developed as an efficient reagent for the oxidation of a variety of functional groups, including alcohols, phenols, amines,

sulfide, carbonyl compounds, *etc.* under mild conditions.^{2a} Indeed, because of its remarkably high chemo-/regio-/stereoselectivity and its environment- and user-friendly character, **1** is considered a uniquely effective reagent for a broad range of organic synthesis.^{2b-d} The first synthesis of **1** by Hartman and Mayer involved the oxidation of 2-iodobenzoic acid (**2**) with potassium permanganate in water at 30 °C, but this process suffered from a low yield of **1** (30–40%) and the by-products of incomplete oxidation include 1-hydroxy-1,2-benziodoxol-3(1*H*)-one (**3**), so that tedious work-up is required (Figure 1a).^{1a} Ninety years later, Dess and Martin developed a greatly improved protocol by modifying Greenbaum's method,^{3a} in which potassium bromate (KBrO₃) was introduced as an oxidant in hot aqueous H₂SO₄ (0.73 M) (Figure 1b).^{3b} This method provides **1** in high yield (>90%) after a simple work-up, but there are several safety concerns: for example, 1) carcinogenicity of KBrO₃, 2) generation of toxic Br₂, and 3) formation of bromate-related impurities with the potential to undergo violent decomposition upon impact and/or heating.^{3c,4} In 1999, these concerns were dispelled by the development of an alternative method using less toxic and safer Oxone (2KHSO₅-KHSO₄-K₂SO₄) in water.⁵ This procedure substantially reduced the amount of explosive impurities and is now considered a standard method for the synthesis of **1** (Figure 1c). However, we have discovered a safer, less expensive and highly reliable alternative method for the preparation of **1** simply by using sodium hypochlorite (NaClO) and carbon dioxide (CO₂) in water. Furthermore, as the only by-product is NaCl, this reaction can be utilized for one-pot synthesis of 1,1,1-triacetoxy-1,2-benziodoxol-3(1*H*)-one (Dess-Martin reagent)^{3a} (**4**) in excellent yield (Figure 1d).

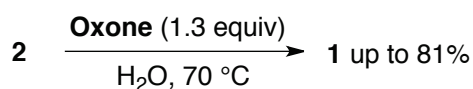
a) First synthesis of IBX **1** using KMnO₄ (since 1893)



b) Improved procedure using KBrO₃ (since 1983)

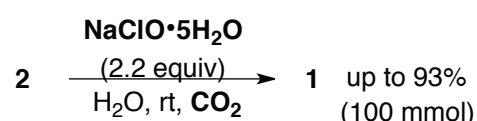


c) Improved procedure using Oxone (since 1999)



d) This work (2020)

• IBX synthesis



• Dess-Martin reagent synthesis

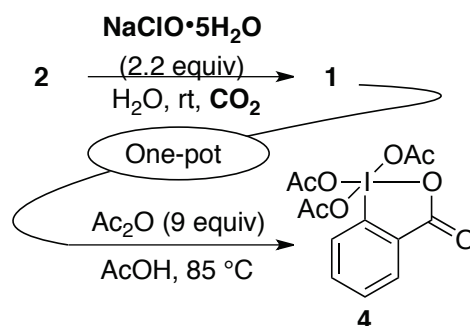


Figure 1. Milestones in the synthesis of IBX **1**, and the present work.

We have recently demonstrated that the activation of $\text{NaClO}\cdot 5\text{H}_2\text{O}$ ⁶ with acetic acid is effective for the oxidation of iodoarenes to trivalent (diacetoxyiodo)arenes.⁷ Unfortunately, this method was not applicable to the preparation of **1**, since trivalent **3** was produced as a major product. In 2005, Zhdankin and co-workers reported an excellent preparation method for pentavalent alkyl 2-iodylbenzoate using 4% aqueous sodium hypochlorite (NaClO) in the presence of an excess amount of dry ice.⁸ Inspired by this result and a report that the disproportionation of NaClO to sodium chlorate (NaClO_3) and sodium chloride is significantly accelerated by CO_2 ,⁹ we decided to examine the oxidation of 2-iodobenzoic acid **2** with $\text{NaClO}\cdot 5\text{H}_2\text{O}$ under carbon dioxide (1 atm). Exposure of iodoarene **2** to 2.2 equivalents of $\text{NaClO}\cdot 5\text{H}_2\text{O}$ in water at room temperature under CO_2 resulted in the slow evolution of foam during the initial ca. 30 minutes, and after 3 hours, IBX **1** was obtained in good yield (Table 1, entry 1). Prolonging the reaction time slightly increased the yield (entry 2). In sharp contrast, the reaction in air (ca. 0.04% CO_2) or in air containing ca. 4% CO_2 did not or scarcely promoted this oxidation (entry 3). Scalability of the synthesis of **1** was demonstrated in the range of 10–100 mmol (entry 4). We did not experience any dangerous events (rapid gas evolution or temperature rise) in the large-scale operations, but we found that the yield was improved when the reaction was started at 0 °C, especially at 100 mmol scale. Use of commercially available 13% aq. NaClO instead of $\text{NaClO}\cdot 5\text{H}_2\text{O}$ gave a comparable yield of **1**, whereas 4% aq. NaClO or $\text{Ca}(\text{ClO})_2\cdot 3\text{H}_2\text{O}$ afforded only moderate to low yield of **1** (entries 5–7). Solvent-free and highly concentrated conditions (3 M) were less effective, probably because of the reduced stirring efficiency of the magnetic stirrer bar under these conditions (entries 8 and 9).

Table 1. Oxidation of 2-iodobenzoic acid **2** with NaClO in water^a

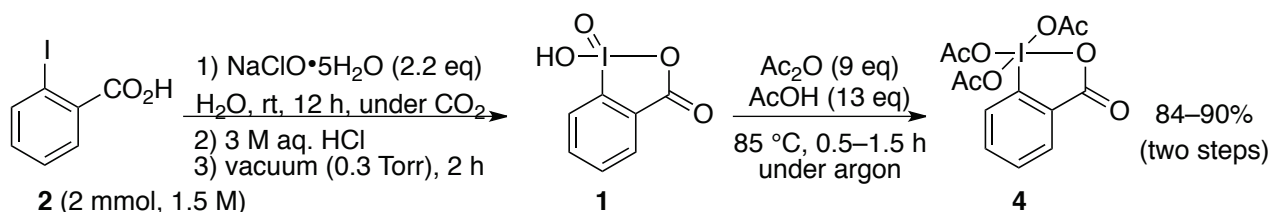
Ic1ccccc1C(=O)O $\xrightarrow[\text{H}_2\text{O, rt, under CO}_2]{\text{oxidant}}$ O=[I](O)c1ccccc1C(=O)O

entry	oxidant (equiv)	time (h)	yield (%) ^b
1	$\text{NaClO}\cdot 5\text{H}_2\text{O}$ (2.2)	3	74
2	$\text{NaClO}\cdot 5\text{H}_2\text{O}$ (2.2)	12	88
3	$\text{NaClO}\cdot 5\text{H}_2\text{O}$ (2.2)	24	46 ^c , 65 ^d
4	$\text{NaClO}\cdot 5\text{H}_2\text{O}$ (2.2)	12	80 ^e , 93 ^{f,g}
5	13% aq. NaClO (2.2) ^h	12	80

6	4% aq. NaClO (2.2) ^h	12	68
7	Ca(ClO) ₂ •3H ₂ O (1.1)	12	12
8 ⁱ	NaClO•5H ₂ O (2.2)	12	54
9 ^j	NaClO•5H ₂ O (2.2)	12	75

^aUnless otherwise noted, 2 mmol of **2** was dispersed in water (1.5 M). ^bIsolated yields. ^cIn air. ^dIn air containing ca. 4% CO₂. ^e10 mmol (2.5 g) scale. ^f100 mmol (25 g) scale. ^gThe reaction was started at 0 °C. ^hCommercially available aqueous NaClO was used. ⁱUnder solvent-free conditions. ^jRun with **2** (3 M).

To our delight, the new strategy could be employed for one-pot direct preparation of Dess-Martin reagent **4**, as the only by-product is NaCl. After reaction of **2** under the optimized conditions (Table 1 entry 2), the reaction mixture was neutralized, washed with water, and dried. In the same flask, **1** was then acetylated with acetic anhydride (9 equiv) in acetic acid at 85 °C to give analytically pure **4** in 90% yield (Scheme 1).^{3a} In contrast, an attempt at direct synthesis of **4** with Oxone instead of NaClO•5H₂O was unsuccessful,⁵ partly because of the formation of large amounts of inorganic acidic by-products, such as KHSO₄.



Scheme 1

In conclusion, our results demonstrate that oxidation of 2-iodobenzoic acid with NaClO•5H₂O under CO₂ is an efficient, convenient and safe method for the synthesis of IBX and Dess-Martin reagent. Key advantages include: 1) easy work-up – filtration of the reaction mixture, followed by washing of the cake with water and acetone on a glass filter was sufficient to afford analytically pure **1**; 2) no formation of harmful/toxic waste – environmentally safe NaCl is a sole by-product; 3) safety – all of the batches of **1** obtained by our procedure were inert when hit with a steel hammer or scraped intensively with a stainless steel spatula.⁴ Further studies on the reaction mechanism and applications are in progress.

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SUPPORTING INFORMATION

Supplementary data (representative experimental procedures and analytical data for reaction products) associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27083/103>

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